The psychophysiology of error and feedback processing in attention deficit hyperactivity disorder and autistic spectrum disorder

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CHAPTER 1

GENERAL INTRODUCTION

STUDY OBJECTIVES

The main question of this thesis is whether children with the developmental disorders Attention Deficit Hyperactivity Disorder (ADHD) or Autism Spectrum Disorder (ASD) have deficits in error and feedback processing and whether they can be discriminated from each other in some aspects of this processing. In the past two decades psychophysiological research has largely extended our knowledge of cortical and autonomic correlates of error and feedback processing in healthy adults, which helps us to understand specific *cognitive control* or *executive functioning* processes. Psychophysiological measurements may, therefore, be useful in exploring differences in specific aspects of these cognitive control or executive functioning processes. To this end both electrocortical and autonomic measures were obtained while children with ADHD or ASD, as well as a typically developing (TD) children, performed cognitive tasks in which feedback on their performance was manipulated.

However, psychophysiological research on error and feedback processing in children is scarce, although recently more and more developmental studies have been published. Moreover, the relation between electrocortical and autonomic measures of error and feedback processing is an under-exposed subject in the literature. A first subquestion of this thesis is, therefore, (how) do electrocortical and autonomic measures of error and feedback processing relate?

The mainstay of ADHD treatment is stimulant medication, mostly Methylphenidate (Mph), which markedly and rapidly reduces the overt clinical manifestations of the syndrome. A second subquestion of this thesis is whether Mph intake in children with ADHD influences the psychophysiology of error and feedback processing.

Finally, a third subquestion is whether specific genetic factors influence the psychophysiology of error and feedback processing. To this end subgroups were formed within the whole tested sample of typically developing (TD) children and children with developmental disorders, based on common functional polymorphisms of two genes, involved in serotonergic and dopaminergic neurotransmission respectively. The variants of these genes have been linked to specific personality traits that have independently from each other been suggested to affect reinforcement-controlled behaviour. This research approach may increase the understanding of natural variations in the

psychophysiology of error and feedback processing, herewith crossing the borders of psychopathological phenotypes.

ERROR AND FEEDBACK PROCESSING

RELEVANCE

A great deal of our acquired behaviour is learnt by attending to feedback on our actions. From birth we are continuously confronted with feedback on our behaviour; as a baby we are praised when we show new behaviour and as we grow a little older we are continuously told what and what not to do by our parents, teachers, peers and other people. Feedback comes to us in different forms; it ranges from a frown or a smile to words of refusal/approval and from tangible rewards or punishments (e.g. money or candy) to more neutral signs that inform us whether we performed correctly or not (knowledge of results). Although feedback is all around us in different forms, we become more and more independent from external feedback by learning from it.

As a child we may rely heavily on feedback from our environment, but as a young adult we grow out to be self-regulatory: most situations around us are well-known and we know what kind of behaviour suits which (social) situation. In well-known situations we will automatically show appropriate and well-adapted (social) behaviour, but when things go wrong or in changing and unknown situations we must overrule our automatic behaviour and we need to increase cognitive control. In these instances it is thus of great importance that we continuously monitor our behaviour/performance and environment, for the purpose of detecting the need for increased cognitive control and for adjustment of behaviour. This executive function (EF) ability is called *performance monitoring*.

This thesis focuses on the monitoring of events that signal the need for increased cognitive control: the commission of error responses and the receipt of negative feedback. The continuous evaluation whether current behaviour is adequate and successful, is the key to appropriately determining and implementing behavioural adjustments. The detection of error responses may allow subjects to alter their response strategy, e.g. by adjusting the speed-accuracy trade-off, while the receipt of negative feedback may be used to leave the currently used inappropriate stimulus-response coupling and shift to one that results in positive feedback.

NEUROBIOLOGY

The past two decades of research on performance monitoring and error processing have largely increased the understanding of the involved neural mechanisms. Based on functional neuroimaging, electrophysiological, lesion and intracranial recording studies, the Anterior Cingulate Cortex (ACC), along with connected prefrontal structures, has been indicated as one of the main brain areas involved in the monitoring of unfavourable outcomes (e.g. negative feedback), error responses, response conflict, and decision uncertainty (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004; Taylor, Stern, & Gehring, 2007). The ACC can be functionally divided into a dorsal region (dACC) that connects with (parts of) the basal ganglia, e.g. striatum, and is involved in motor and cognitive processes, and a rostral region (rACC) that interacts with paralimbic and limbic regions, such as the amygdala and insula, and mediates more emotional processes (Bush, Luu, & Posner, 2000; Phillips, Drevets, Rauch, & Lane, 2003). Both regions of the ACC show increased activation in response to errors (Carter et al., 1998; Kiehl, Liddle, & Hopfinger, 2000) and have been identified as potential neuronal sources of error-related Event-Related Potentials (Dehaene, Posner, & Tucker, 1994b; Luu, Tucker, Derryberry, Reed, & Poulsen, 2003; van Veen & Carter, 2002; Mathalon, Whitfield, & Ford, 2003; Miltner et al., 2003). A recent review by Taylor and colleagues (2007) states that both the dACC/ prefrontal Medial Frontal Cortex (pMFC) and rACC/lateral Prefrontal Cortex (PFC) are convincingly involved in error processing.

According to a recent theory by Holroyd and Coles (2002) the role of the dACC in error and feedback processing may be explained in terms of a common functional and neurobiological mechanism that codes events according to the reinforcement learning principle (Schultz, 2000). Following error commission the dACC implements error-based reinforcement learning using phasic dopaminergic signals from the striatum and mesencephalic dopamine system. Phasic increases of DA activity in the basal ganglia code for events that are unexpectedly better than expected, while phasic decreases code for events that are suddenly worse than expected. As these phasic changes in DA activity are conveyed to the dACC, these reward and error signals can be used to identify and select appropriate behaviours and thereby improving performance (Holroyd & Coles, 2002). Error-related activity of the rACC has been proposed to reflect appraisal of the affective or motivational significance of errors (Luu et al., 2003; Taylor

et al., 2007; van Veen & Carter, 2002). The rACC likely fulfils this role in conjunction with the insula and amygdala, as these structures are densely interconnected with the rACC (Van Hoesen, Morecraft, & Vogt, 1993) and become increasingly active during error processing (Menon, Adleman, White, Glover, & Reiss, 2001; Taylor et al., 2007; Brazdil et al., 2002; Garavan, Ross, Murphy, Roche, & Stein, 2002).

PSYCHOPHYSIOLOGY

Since the early nineties ElectroEncephalogram (EEG) Event-Related Potential (ERP) studies in humans have identified several electrocortical components reflecting error and feedback processing. Moreover, heart rate (HR) has also been found sensitive to performance monitoring activity. As these psychophysiological measures are the central point of this thesis they are briefly introduced here.

The error-related EEG component that has received most attention in performance monitoring literature is the *Error-Related Negativity* (ERN: Gehring, Coles, Meyer, & Donchin, 1990; Gehring, Goss, Coles, Meyer, & Donchin, 1993; Ne: Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991). A similar component occurs when negative feedback is processed: the *feedback ERN* (Medial Frontal Negativity: Gehring & Willoughby, 2002; Feedback ERN: Holroyd & Coles, 2002; Feedback Related Negativity: Müller, Möller, Rodriguez-Fornells, & Münte, 2005; Holroyd & Coles, 2002; Holroyd, Larsen, & Cohen, 2004a). These components reflect the first warning signal that ongoing behaviour is no longer appropriate and that increased cognitive control is needed (Holroyd & Coles, 2002; Nieuwenhuis, Ridderinkhof, Blow, Band, & Kok, 2001; Brown & Braver, 2005). Source localisation studies point to the ACC as the main neuronal source of the ERN (Taylor et al., 2007). Both components may represent a phasic decrease of dopaminergic firing to the dACC (Holroyd & Coles, 2002).

Further error processing may be reflected by the *error Positivity (Pe)*, which is a positive-going potential that follows the ERN (Falkenstein et al., 1991; Davies, Segalowitz, Dywan, & Pailing, 2001). Some studies indicate that the amplitude of the Pe, but not the ERN, covaries with awareness of the error (see for a review: Overbeek, Nieuwenhuis, & Ridderinkhof, 2005) and that the Pe, but not the ERN, is associated with the strategic slowing of response time after errors (post error slowing) (Hajcak, McDonald, & Simons, 2003b; Nieuwenhuis et al., 2001). Several authors have noted similarities between the Pe and the stimulus-related P3 (Davies et al., 2001; Leuthold &

Sommer, 1999a; O'Connell et al., 2007; Overbeek et al., 2005; Jonkman, Van Melis, Kemner, & Markus, 2007). As the P3 has been linked to phasic responses of the locus coeruleus-noradrenaline (LC-NE) system (Nieuwenhuis, Aston-Jones, & Cohen, 2005), conscious error processing may, therefore, be associated with increased phasic activity of the noradrenergic system.

Regarding feedback processing, successive to the feedback ERN a P3 is elicited (Miltner, Braun, & Coles, 1997), which may reflect the processing of relevant information that can be used to modify future behaviour (Müller et al., 2005). Literature is inconsistent as to whether the feedback P3 amplitude is larger for positive or negative feedback, but in general the P3 is known to increase when (1) the subjective probability of the stimulus is low, (2) the motivational significance of the stimulus is high and (3) the amount of attention paid to the stimulus is high (for a review see: Nieuwenhuis et al., 2005). Another relevant component that has been designated as the affective counterpart of the classical P3 is the Late Positive Potential (LPP). The LPP is elicited by highly arousing pleasant and unpleasant pictures compared to neutral pictures and is thought to reflect increased attention to affective-motivational stimuli (Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000b; Hajcak & Olvet, 2008; Hajcak, Moser, & Simons, 2006; Schupp et al., 2000b). It has been hypothesised that this component reflects facilitated or amplified stimulus processing resulting from amygdala-activity (Hajcak et al., 2006; Bradley et al., 2003a).

The prefeedback Stimulus Preceding Negativity (SPN) has also been described in relation to feedback monitoring. The prefeedback SPN is a negative-going slow wave that has been associated with the anticipation of the affective motivational value of feedback stimuli (for an overview see: Böcker, Baas, Kenemans, & Verbaten, 2001). The prefeedback SPN is, for example, larger in preparation of rewarding feedback opposed to non-rewarding feedback and larger in preparation of informative opposed to uninformative feedback (Kotani, Hiraku, Suda, & Aihara, 2001; Chwilla & Brunia, 1991). The insular cortex, which is intimately connected with the limbic system, has repeatedly been suggested to be one of the main neural generators of the prefeedback SPN (Böcker, Brunia, & Van den Berg-Lenssen, 1994; Brunia, De Jong, Van den Berg-Lenssen, & Paans, 2000; Tsukamoto et al., 2006). The prefeedback SPN amplitude

may, therefore, be the reflection of the subject's motivational involvement in the task (Bastiaansen, Böcker, & Brunia, 2002).

Performance monitoring processes are also reflected by autonomic measures. First of all, heart rate (HR) decelerates briefly in anticipation and preparation of upcoming feedback stimuli (see the review by: Jennings & Van der Molen, 2002). This concerns brief beat-to-beat increases in the time between heartbeats (Inter Beat Intervals: IBIs) that can be observed by selecting IBI times around feedback stimuli and computing averages of the resulting IBI patterns across feedback conditions (for example positive and negative feedback). The resulting pattern of IBIs is called *Evoked Heart Rate (EHR)*. Whereas positive feedback immediately elicits an acceleratory recovery at feedback onset, negative feedback elicits a prolonged or enhanced EHR deceleration (Crone et al., 2003c; Somsen, Van der Molen, Jennings, & Van Beek, 2000; Van der Veen, Van der Molen, Crone, & Jennings, 2004). Similar enhanced EHR decelerations are also elicited by error responses (Crone, Somsen, Zanolie, & Van der Molen, 2006; Hajcak et al., 2003b; Hajcak et al., 2003b).

DEVELOPMENTAL CHANGES

Developmental psychophysiological studies in children and adolescents have established that the ability of performance monitoring grows with age. As this thesis concerns 10-to 12-year-old children, the impact of typical development on the relevant psychophysiological measures will be shortly addressed here.

The ERN amplitude in school-aged children is substantially smaller than in young adults and its amplitude develops throughout the second decade of life (Davies, Segalowitz, & Gavin, 2004; Hogan, Vargha-Khadem, Kirkham, & Baldeweg, 2005; Santesso, Segalowitz, & Schmidt, 2006). The Pe seems to follow a different developmental trajectory; two studies have indicated that school-aged children show Pe amplitudes similar to young adults (Davies et al., 2004; Santesso et al., 2006). With regard to EHR measures of error processing, a developmental study by Crone and colleagues (2006) showed that 8- to 10-year-old children show no EHR deceleration after error responses, while 12- to 14-year-old children and 16- to 18-year-old adolescents do. This suggests that with increasing age children become able to online monitor their behaviour. Moreover, another developmental EHR study has indicated that preadolescents do not process feedback information as efficient as adults (Crone,

Jennings, & Van der Molen, 2004). While 12-year-old children and adults showed differentiated EHR responses to different types of feedback stimuli, 8- to-10-year-old children showed undifferentiated EHR responses. These developmental findings on error and feedback processing can be related to the relatively slow maturation until early adulthood of the frontal lobes in general (Stuss, 1992) and the ACC in particular (Cunningham, Bhattacharyya, & Benes, 2002; Eshel, Nelson, Blair, Pine, & Ernst, 2007; Davies et al., 2004; Santesso et al., 2006).

(HOW) DO ELECTROCORTICAL AND AUTONOMIC CORRELATES OF ERROR AND FEEDBACK PROCESSING RELATE?

Heart rate deceleration in response to performance feedback has been suggested to be a reflection of the same error monitoring system that is at the basis of the ERN (Somsen et al., 2000; Jennings & Van der Molen, 2002; Crone et al., 2003c). This suggestion is supported by findings of shared functional characteristics on the one hand, and by findings of a shared neural substrate on the other. It is, for example, quite well established that the dorsal ACC, which is involved in the generation of the ERN, also forms part of a system that generates changes in autonomic state during effortful cognitive processing (for a review see: Critchley, 2005). A study by Hajcak and colleagues (2003b), however, failed to find a significant correlation between error-related heart rate deceleration and the ERN. These authors, however, did report on a positive correlation between the Pe amplitude and subsequent skin conductance response activity and suggested that the Pe triggers the subsequent autonomic nervous system (ANS) activity. They concluded that the full range of performance monitoring processes may rely on the interplay of centrally generated signals, affecting both decision-making systems in the brain and peripheral changes in body state (Hajcak et al., 2003b).

The first subquestion this thesis deals with, is whether different error- and feedback-related ERP components are interrelated with simultaneously measured heart rate responses to those events. Answers were sought by both investigating their functional characteristics during a feedback-based learning task and by directly computing correlations between the ERP components and EHR responses in a sample of typically developing preadolescent children.

CAN ADHD AND ASD BE DISCRIMINATED ON THE PSYCHOPHYSIOLOGY OF ERROR AND FEEDBACK PROCESSING?

ADHD, ASD AND THEIR OVERLAP

ADHD is a disorder characterised by a persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequent and severe than is typically observed in individuals at a similar level of development. ADHD is regarded as one of the most common psychiatric disorders of childhood and has been estimated to affect 3%-7% of school-aged children worldwide (American Psychiatric Association, 2000). The symptoms must be present during at least six months and some impairment must have been present before the age of 7 years. Moreover, some impairment from the symptoms must be present in at least two settings (e.g. at home and at school). Three subtypes of ADHD are distinguished in the DSM-IV-TR: the predominantly inattentive, the predominantly hyperactive/impulsive and the combined type. The latter is by far the most common.

Children with ADHD have numerous difficulties in both structured situations, such as the classroom, and unstructured situations, such as the playground, that impair the affected individuals and disturb their fellow humans. The hyperactive and impulsive symptoms are the most outstanding characteristic of children with ADHD, finding expression in shouting out replies, interrupting others, being reckless and accident-prone. Less outstanding, however not less impairing, are the inattention symptoms, which are manifested by, for example, difficulties with attending to instructions in academic and social situations and being poorly organized and forgetful. ADHD is designated as a heterogeneous disorder, because the symptoms vary both within and between individuals. Within individuals the ADHD behaviour may be rather context-dependent, for example a child with ADHD may be distractible and inattentive in the classroom, but restless and impulsive at home. Between individuals there is large variability in symptom presentation, severity and comorbid conditions.

Autistic Disorder is defined by the early onset of a ‘triad of deficits’ (Wing & Gould, 1979): impaired development in social interaction and communication and a markedly restricted repertoire of activity and interests (American Psychiatric Association, 2000). The most characteristic aspects of individuals with Autistic Disorder concern gross and sustained impairment in reciprocal social interaction and the ability to form and

maintain relationships (Tanguay, Robertson, & Derrick, 1998). Abnormalities in verbal and nonverbal communication concern difficulties in carrying on conversations and social chat, its most distinctive feature being its lack of, or unusual, social quality (Jarrold, Boucher, & Russell, 1997). Individuals with Autistic Disorder often show a delay in, or a total lack of, the development of spoken language and often use stereotyped, repetitive or idiosyncratic language. Finally, individuals with Autistic Disorder also show restrictive, repetitive and stereotyped patterns of behaviour, interests and activities. This often concerns unusual preoccupations and circumscribed interests that are abnormal in intensity or focus, adherence to non-functional routines or rituals and/or stereotyped movements and activities.

The umbrella term Autistic Spectrum Disorders (ASDs) is used to cover a broader range of autistic-like disorders. It includes individuals showing 'atypical autism' that do not meet the criteria for Autistic Disorder because of late age onset, atypical symptomatology, or subthreshold symptomatology, or all of these. These individuals are classified as Pervasive Developmental Disorder Not Otherwise Specified (PDDNOS). No positive criteria have been formulated for this disorder, although the diagnosis requires severe and pervasive impairment of Autistic Disorder symptoms (American Psychiatric Association, 2000). Prevalence rates of ASD depend on the definition of the disorder, but estimates that also include PDDNOS range from 30 to 60 cases per 10.000 individuals (Fombonne, Zakarian, Bennett, Meng, & Lean-Heywood, 2006; Rutter, 2005). This thesis describes children that had been diagnosed as having PDDNOS, who will be referred to as children with ASD.

Although ADHD and ASD are described as clearly distinct disorders, in clinical practice it often appears difficult to discriminate between the two (Clark, Feehan, Tinline, & Vostanis, 1999; Jensen, Larrieu, & Mack, 1997). Phenomenological studies report that many children with ADHD also have ASD symptoms and vice versa (see for a review: Nijmeijer et al., 2008). Many children with ADHD show inadequate social behaviours that are crucial for their prognosis (Greene et al., 1996; Greene, Biederman, Faraone, Sienna, & GarciaJetton, 1997). These children are characterised by a limited repertoire of social responses and a lack of comprehension of the impact of their actions on others (Nijmeijer et al., 2008). The most frequently reported ASD symptoms in children with ADHD are impairments in social interaction and a lack of awareness of

feelings and thoughts of others (Buitelaar, Van der Wees, Swaab-Barneveld, & Van der Gaag, 1999; Santosh & Mijovic, 2004; Clark et al., 1999; Nijmeijer et al., 2008). The other way around, children with ASD often display symptoms of ADHD (Ghaziuddin, Weidmer-Mikhail, & Ghaziuddin, 1998; Goldstein & Schwebach, 2004; Keen & Ward, 2004; Lee & Hinshaw, 2006; Yoshida & Uchiyama, 2004; Nijmeijer et al., 2008). Some children with ASD have for instance been found to score as high as children with ADHD on hyperactivity and acting out behaviour and have been found to even fulfil all criteria for the diagnosis of ADHD (Jensen et al., 1997; Frazier et al., 2006).

Moreover, both ADHD and ASD have been related to executive functioning deficits (Barkley, 1997; Pennington & Ozonoff, 1996; Russell, 1997). Intact Executive Functions (EFs) enable individuals to show goal-directed behaviour that is flexibly adapted to the environment. EF deficits may, therefore, hamper children with ADHD and ASD in self-regulatory capabilities in everyday life. There is, however, an ongoing debate on the type of EF profile that is specific for either disorder (Sergeant, Geurts, & Oosterlaan, 2002; Geurts, Vertie, Oosterlaan, Roeyers, & Sergeant, 2004; Happé, Booth, Charlton, & Hughes, 2006; Ozonoff & Jensen, 1999). Studies directly comparing the performance of children with ADHD and children with ASD on neuropsychological tasks tapping distinct domains of executive functioning, have suggested that children with ADHD show greater deficits in response inhibition, while children with ASD show marked deficits in planning, flexibility and response selection/monitoring (Ozonoff & Jensen, 1999; Geurts et al., 2004; Happé et al., 2006, but see for a different finding Nyden, Gillberg, Hjelmquist, & Heiman, 1999). Although neuropsychological tasks may be closely related to complex tasks in everyday life and, therefore, have large ecological validity, one major limitation of their use is that the performance measures reflect the outcome of multiple underlying component processes.

The main question of this thesis with respect to these issues is whether ASD and ADHD show distinct deficits in component processes of EF, specifically in the area of monitoring errors and feedback. The use of psychophysiological measures allows for separating specific cognitive control processes and, consequently for making inferences about their underlying neurobiological sources.

ERROR AND FEEDBACK PROCESSING IN ADHD

The firstly stated symptom of inattention in the DSM-IV, and subject of this thesis, is that a child with ADHD 'often fails to give close attention to details or *makes careless mistakes in schoolwork, work, or other activities*' (American Psychiatric Association, 2000, p. 92). Children with ADHD seem to have difficulties in interrupting their actions and in adjusting incorrect or maladaptive responses, which finally results in the commission of careless errors. This suggests that error and feedback processing deficits are inherent to ADHD.

Influential comprehensive models of ADHD have advocated that disinhibition is central to the disorder, and distinguishes it from other disorders (Barkley, 1997; Quay, 1988a; Quay, 1988b). The inhibitory deficits result in a failure to delay responding and can be regarded as a cognitive deficit, i.e. a deficit of EFs. Other comprehensive models of ADHD suggest that the disorder is characterised by an altered motivational style (Haenlein & Caul, 1987; Douglas & Parry, 1994) or at least by the interplay of cognitive and motivational deficits (Sonuga-Barke, 2002; Sergeant, 2000; Sagvolden, Johansen, Aase, & Russell, 2005a). Motivational deficits in ADHD may be expressed by a deficient sensitivity to reinforcement, including aberrant reward and/or punishment sensitivity and decreased sensitivity, or aversion, to delay of reward (Haenlein & Caul, 1987; Quay, 1988a; Quay, 1988b; Douglas & Parry, 1994; Sergeant, 2000; Sonuga-Barke, 2002; Sagvolden et al., 2005a; Rapport, Tucker, Dupaul, Merlo, & Stoner, 1986; Carlson, Mann, & Alexander, 2000; Carlson & Tamm, 2000). Although literature on motivational deficits in ADHD mainly concerns reward-related processes, subjects with ADHD have also been suggested to show diminished sensitivity to negative feedback, such as punishment and absence of reward (Carlson et al., 2000; Carlson & Tamm, 2000; Douglas & Parry, 1994; Quay, 1988a; Quay, 1988b).

Neurobiological animal models of ADHD have linked the meso-limbic dopamine pathways that are associated with the reward circuit in the brain to the motivational deficits in ADHD (Sagvolden et al., 2005a; Sonuga-Barke, 2002). Meso-cortical dopamine pathways on the other hand have been linked to the deficient inhibitory control, i.e. the cognitive deficits in ADHD (Sagvolden et al., 2005a; Sonuga-Barke, 2002). Although the distinction between cognitive and motivational deficits is theoretically useful, they are linked functionally and neurobiologically (Nigg, 2001).

Both theories point to interconnected neural systems of the basal ganglia and prefrontal cortex. An important structure, serving as a 'bridge' between lower brain systems, like the basal ganglia and the limbic system, and the prefrontal cortex is the ACC. This structure is suggested to be involved in both 'hot' (motivational, affective, emotional) and 'cool' (cognitive) regulation processes (Bush et al., 2000). The ACC is suggested to be involved in the processing of both errors and feedback (Taylor et al., 2007). Investigating electrocortical responses during error and feedback processing may, therefore, provide insight into regulation processes that integrate cognitive and motivational explanations of ADHD.

The majority of performance studies on feedback processing in ADHD have revealed that feedback on the performance of children with ADHD has a positive effect on their task performance and self-reported motivation, this effect being more prominent than in TD children (see for a review: Luman, Oosterlaan, & Sergeant, 2005). However, children with ADHD may have problems in keeping optimal performance when they have to rely solely on their intrinsic motivation (Douglas & Parry, 1994; Sergeant, 2000; Luman et al., 2005).

Few studies have investigated psychophysiological measures of error and feedback processing in ADHD. One ERP study in ADHD children suggests an initial enhanced sensitivity to negative feedback (enhanced feedback ERN), but diminished further evaluation of feedback information (decreased later positivity) (Van Meel, Oosterlaan, Heslenfeld, & Sergeant, 2005b). Unpublished work by Van Meel, Heslenfeld, Oosterlaan, Luman & Sergeant (2005) showed that children with ADHD anticipate feedback stimuli to a lesser extent in comparison to TD children (decreased prefeedback SPN). EHR studies point to a diminished physiological sensitivity to feedback stimuli in general (Luman, Oosterlaan, Hyde, Van Meel, & Sergeant, 2007; Luman, Oosterlaan, & Sergeant, 2008; Crone, Jennings, & Van der Molen, 2003a) and a diminished discrimination between positive and negative feedback in particular (Crone et al., 2003a). Regarding ERP studies on the processing of error responses, the findings on ERN amplitude in children with ADHD vary widely (Liotti, Pliszka, Perez, Kothmann, & Woldorff, 2005a; Van Meel, Heslenfeld, Oosterlaan, & Sergeant, 2007; Jonkman et al., 2007; Wiersema, Van der Meere, & Roeyers, 2005; Burgio-Murphy et al., 2007). To date the Pe amplitude is fairly consistently found to be reduced in children with ADHD

(Jonkman et al., 2007; Overtoom et al., 2002a; Wiersema et al., 2005, but see for a different finding Burgio-Murphy and colleagues, 2007).

ERROR AND FEEDBACK PROCESSING IN ASD

One of the most influential comprehensive theories of the social difficulties in Autistic Disorder is the Theory of Mind (ToM) deficit hypothesis (Baron-Cohen, Leslie, & Frith, 1985; Frith, 1989). This theory states that autistic individuals suffer from 'mind-blindness', disabling them in understanding other people's beliefs and desires, and in using this knowledge for predicting the behaviour of others. The ability to adequately ascribe mental states to others is also referred to as 'mindreading' or 'mentalising' (Frith & Frith, 2001). Although it has been demonstrated that ToM deficits are not specific to Autistic Disorder, the ToM theory has been accepted as important to the understanding of its social deficits (see for a review: Happé, 1994).

Another influential theory proposes that deficits in the EFs underlie many of the key characteristics of autism (Pennington & Ozonoff, 1996; Russell, 1997; see for a review: Hill, 2004). Since the emergence of the executive dysfunction theory of autism, ToM deficits in Autistic Disorder have been explained by EF deficits. It has been argued that the development of executive functions allows the child's ToM to develop and that performance on ToM tasks can even be reduced to executive function ability (see for a review: Hill, 2004). By reviewing the EF deficit theory of Autistic Disorder, Hill (2004) concludes that EF deficits may next to non-social characteristics, such as rigidity and perseveration, explain the social characteristics of the disorder as well. However, she also stresses the need for clearer EF profiles, which can be fulfilled by 'fractionating' the executive system and its dysfunction in autism. Investigating component processes of error and feedback processing in ASD may, thus, gain insight into specific EF deficits in this disorder.

Recently, the ACC has been shown to become active when normal subjects either attribute mental states to themselves or others (Frith & Frith, 2001; Amodio & Frith, 2006; Mundy, 2003). Various other social cognition tasks, involving self-knowledge or person perception activate the (r)ACC as well (see for a meta-analysis: Amodio & Frith, 2006). In line with the profound difficulties of subjects with Autistic Disorder on the performance of mentalising tasks, several neuroimaging studies have found support for a hypofunctional ACC (Haznedar et al., 2000; Ohnishi et al., 2000; Gomot et al., 2006).

Two of these studies, moreover, report that ACC activity is negatively associated with symptom presentation in autism (Haznedar et al., 2000; Ohnishi et al., 2000). The ACC may thus, next to error and feedback monitoring, also be involved in the processing of high level abstract representations that play a major role in social cognition. Deficits in ACC functioning may hamper subjects with ASD in (1) monitoring errors and feedback and, accordingly, in flexibly adapting to changing environments, and (2) attributing mental states to themselves or others, and, accordingly, in developing social adequate behaviour.

Some performance studies have found evidence for an error correction impairment in ASD. Russell and Jarrold (1998) found that autistic children have a deficit in the correction of error responses, both when they are provided with visual feedback about their errors and when they have to detect their errors themselves. Bogte and coll

eagues (2007), moreover, showed absent post error slowing in a group of adult subjects with Autistic Disorder, whereas the control group substantially adjusted their reaction time after errors. Performance studies on feedback processing revealed that children with ASD perform worse than TD children when receiving social feedback, but not with non-social feedback (e.g. sensory or tangible) (Garretson, Fein, & Waterhouse, 1990; Dawson et al., 2002; Ingersoll, Schreibman, & Tran, 2003). One study by Althaus and colleagues, however, showed that children with ASD have more difficulties than TD children in keeping up performance in a sustained attention task despite the provided performance feedback (Althaus, De Sonneville, Minderaa, Hensen, & Til, 1996).

To date only one ERP study has investigated performance monitoring ability in ASD by Henderson and colleagues (Henderson et al., 2006). This study could not reveal overall differences in ERN amplitude between ASD and TD children. Larger ERN amplitudes in the ASD group, however, were predictive of a smaller impairment in social interaction as well as of less internalising problems.

Given the overlap in problem behaviour between the two disorders in clinical practice as well as overlap in some EF deficits in both disorders, it is useful to directly compare children with both disorders on component processes of EFs. Psychophysiological measures may be a tool for 'fractionating' the executive system and refining research into EF deficits in these disorders (see: Hill, 2004). To date psychophysiological

research on error and feedback processing in ADHD is rather inconsistent and research in this topic in ASD is scarce. Therefore, one of the main questions of this thesis is whether children with ADHD and children with ASD can be discriminated on the psychophysiology of error and feedback processing.

DOES METHYLPHENIDATE STIMULATE ERROR AND FEEDBACK PROCESSING IN ADHD?

The mainstay of ADHD treatment is the prescription of low dose stimulant medication, such as Methylphenidate (Mph; Ritalin®) and dexamphetamine. Non-pharmacologic psychosocial therapies, such as behavioural and cognitive-behavioural therapy, are not as effective as stimulants in reducing the core ADHD symptoms (The MTA Cooperative Group, 1999; see for a recent meta-analysis: Van der Oord, Prins, Oosterlaan, & Emmelkamp, 2008). Numerous placebo-controlled randomized studies have given evidence that stimulant medication markedly and rapidly reduces the overt clinical symptoms of ADHD such as restlessness, inattentiveness and impulsiveness (see for meta-analyses: Miller, 1999; Jadad et al., 1999). The effect on neuropsychological measures is also evident (although less robust as the effect on overt symptoms). Stimulants have for example been shown to increase task accuracy and focussed attention in search tasks and decrease impulsive responses in subjects with ADHD (Douglas, Barr, Desilets, & Sherman, 1995; Tannock, Schachar, & Logan, 1995; Brumaghim & Klorman, 1998). These effects of low dose Mph on EFs are the result of its stimulating effect on prefrontal catecholamine neurotransmission, especially dopamine and noradrenaline (Arnsten, 2006; Pliszka, 2005; Seeman & Madras, 1998).

Regarding error processing, Mph is found to increase remedial action after error commission: RT slowing after error trials increases in children with AD(H)D (De Sonneville, Njiokiktjien, & Bos, 1994a; Krusch et al., 1996b). In accordance with this finding, one small placebo-controlled study found that Mph normalises the Pe amplitude in children with ADHD (Jonkman et al., 2007).

Given that Mph stimulates prefrontal catecholamine neurotransmission, which is also involved in error and feedback processing, and some evidence of improved error processing in Mph-treated children with ADHD, the second subquestion of this thesis is whether Mph stimulates the psychophysiological responses to errors and feedback in children with ADHD.

DO SPECIFIC GENETIC FACTORS INFLUENCE THE PSYCHOPHYSIOLOGY OF ERROR AND FEEDBACK PROCESSING?

Behavioural genetic studies provide strong evidence that psychiatric disorders have a substantial genetic component (Sanders, Duan, & Gejman, 2004). However, due to the large heterogeneity and complexity of psychiatric phenotypes it is (1) difficult to pinpoint specific genes that contribute to psychiatric syndromes as well as (2) to link specific genes to behaviour (Faraone et al., 2005). *Endophenotypes*, or phenotypes that are more closely linked to the neurobiological substrate of a disorder, offer the potential to address these two issues simultaneously (Freedman, Adler, & Leonard, 1999). Abnormal functioning performance monitoring mechanisms may underlie cognitive and behavioural deficits across a range of disorders and personalities. As a consequence, psychophysiological measures of error and feedback processing may serve as endophenotypes for genetic studies of psychopathology.

The third subquestion of this thesis is whether specific genetic factors influence the psychophysiology of error and feedback processing, herewith making a start in elucidating the genetics of performance monitoring. Answers are sought by investigating the relationship between polymorphisms of two genes and several ERP components related to error and feedback processing in a, with respect to psychopathology, heterogeneous sample of children. In specific, common polymorphisms of two genes, the serotonin transporter (5-HTTLPR) gene and the D2 dopamine receptor (DRD2/ANKK1) gene, are investigated that have in common that they have both been associated with a predisposition to alcoholism (Wu et al., 2008).

Although the field needs expansion, several studies indicate that ERP components of error processing are influenced by genetic factors. Recently, a twin study has indicated that individual differences in the response-locked ERN and Pe for example, are highly heritable (Anokhin, Golosheykin, & Heath, 2008). One study by Falgatter and colleagues explored the association between the ERN/Pe and the common polymorphisms of the 5-HTTLPR gene (Fallgatter et al., 2004). These authors reported an enhanced ERN amplitude, and a trend in the same directions for the Pe, in carriers of the low-activity short variant of this polymorphism compared to carriers of the long variant. Individuals carrying the short variant have repeatedly been suggested to be prone to anxiety-related personality traits (Brown & Hariri, 2006; Jacob et al., 2004;

Sen, Burmeister, & Ghosh, 2004), to show augmented neural processing of aversive stimuli (Canli et al., 2005), and greater sensitivity to stimuli associated with punishment (Finger et al., 2007). With regard to the common polymorphisms of the DRD2 gene to our best knowledge no studies have directly investigated error- or feedback-related ERPs. The DRD2 Taq1A1 allele has been related to the Reward Deficiency Syndrome, pointing to an inefficiency in the acquired reward system. Carriers of this allele may, therefore, be less sensitive to positive feedback than noncarriers.

Next to making a start to elucidate genetic factors influencing error and feedback processing, the adopted research strategy may also provide insight into the natural variations in error and feedback processing style. Previous research has for example shown that individuals with different personality types exhibit different electrophysiological responses to errors. Leaving the circumscribed psychopathological phenotypes may thus increase the understanding of natural, genetically determined, variations in error and feedback processing.

OUTLINE OF THIS THESIS

CHAPTER 2 describes electrocortical (ERP) and autonomic (EHR) measures of error and feedback processing in 10- to 12-year-old TD children and the dynamics of these measures during feedback-based learning. This chapter provides insight into the component processes of normal error and feedback processing in children and, moreover, provides insight into the relationship between cortical and autonomic measures of performance monitoring. This chapter serves as a basis for CHAPTER 3, in which the same electrocortical measurements are applied in the comparison of children with ADHD and children with ASD. It focuses on the dissociation of these two developmental disorders on performance monitoring ability and provides more detail on the (dysfunctional) neurobiological basis of the performance monitoring components. CHAPTER 4 describes autonomic (EHR) responsiveness to feedback stimuli in nearly identical samples as described in CHAPTER 3. In this chapter, a paradigm was adopted in which three different feedback approaches were administered to the children (neutral, reward and punishment). This chapter also aims at dissociating children with ADHD from children with ASD, but focuses on the autonomic sensitivity to feedback. CHAPTER 5 describes variations in electrocortical (ERP) measures of error and feedback processing due to two common functional polymorphisms of respectively the serotonin

transporter gene (5-HTTLPR) and the D2 dopamine receptor gene (DRD2). This chapter aims at elucidating the genetic basis of component processes of performance monitoring. This research approach is helpful for the identification of endophenotypes of psychopathology and may, therefore, eventually increase our understanding of the genetic basis of psychiatric diseases. Finally, CHAPTER 6 presents a summary of the main findings, the general conclusions and discusses possible implications for further research and clinical practice.